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# Analytical First Derivatives of Molecular Surfaces with Respect to Nuclear Coordinates

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## ABSTRACT

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We present analytical expressions for the first derivatives of area and other geometrical quantities of polygonal tesserae defined on molecular surfaces. This is a necessary step in the calculation of free energy derivatives with respect to nuclear coordinates for molecular solutes, in the framework of the polarizable continuum method. An application to solute-solvent dispersion energy derivatives is presented. © 1996 by John Wiley & Sons, Inc.

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## Introduction

Analytical expressions of energy derivatives with respect to nuclear coordinates for molecules embedded in a dielectric continuum have been recently presented<sup>1</sup>. Such expressions refer to a model (polarizable continuum model, PCM)<sup>2,3</sup> in which the solvent is a continuum infinite medium, with a cavity of realistic molecular shape containing the solute molecule. In this model the surface of the cavity is tessellated into spherical polygons<sup>4</sup>. The solute-solvent electrostatic interaction is described with a set of polarization

point charges, placed in the center of each tessera. The magnitude of the polarization charges depends not only on the electrostatic potential due to the solute molecule but also on geometrical parameters referred to each tessera (i.e., area, center position, and unit vector normal to the cavity surface).<sup>2</sup> Analytical derivatives of these geometrical quantities with respect to nuclear coordinates are needed to calculate the energy derivatives. The present work reports general expressions for the derivatives of tesserae geometrical parameters, with an example of application to the solute-solvent dispersion and repulsion energy.

At present, a number of analytical methods are available to calculate the area of a molecular surface (and the enclosed volume, too)<sup>5-15</sup>. Some

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methods provide a tessellation scheme,<sup>8,11</sup> and some allow also the calculation of the derivatives of the molecular surface area and of the molecular volume with respect to nuclear coordinates,<sup>5,13,15</sup> but none provides the derivatives of the area of single tesserae.

To obtain our expressions, we have introduced some changes in the routine GEPOL, used in the PCM procedure to build up the cavity as a set of interlocking spheres. A brief survey of the revised GEPOL procedure is presented, the expressions of the derivatives are obtained, and the application to the dispersion energy derivatives is reported.

### Revised GEPOL Procedure

The definition of the cavity and its subdivision in tesserae by GEPOL has been described elsewhere.<sup>16-18</sup> Recently, a comparison between GEPOL and other methods has appeared in a review<sup>19</sup> devoted to a detailed analysis of continuum solvation models.

Starting from van der Waals spheres centered on the solute atoms, the GEPOL procedure can describe three different kinds of molecular surfaces: the proper van der Waals surface, the accessible surface, and the solvent excluding surface (Fig. 1). The accessible surface is defined as the surface generated by the center of a rigid probe sphere rolling on the van der Waals surface; the solvent excluding surface is the envelope of the volume extended to the probe sphere when it rolls on the van der Waals spheres centered on the solute atoms; this latter definition corresponds to the molecular surface defined by Richards.<sup>20</sup>

Among these different definitions, the solvent excluding surface is the best choice for calculating electrostatic solute-solvent interactions in the framework of PCM, while nonelectrostatic interactions (i.e., cavitation and dispersion solute-solvent energies) are described better with accessible surfaces. The computational procedure presented in this work will be used for analytical calculation of the derivatives of electrostatic and nonelectrostatic solute-solvent interaction energies. Thus we shall find expressions for the derivatives of tesserae geometrical parameters both in the case of accessible surfaces and in the case of solvent excluding surfaces.

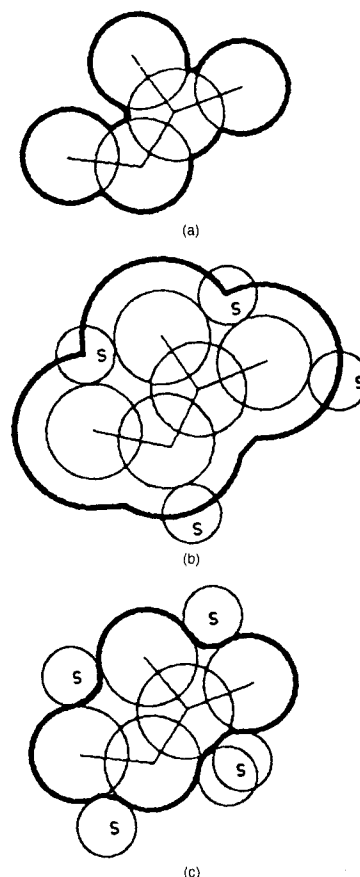
Let us recall briefly the method of added spheres used by GEPOL to approximate the reentrant parts of the solvent excluding surfaces, as this point is

relevant in the following. The procedure starts, as said earlier, placing a sphere, with a suitable radius, around each atom of the solute. When a couple of these atomic spheres are close enough to exclude the solvent from the space between them, GEPOL adds some other spheres, not centered on atoms, as shown in Figure 2.

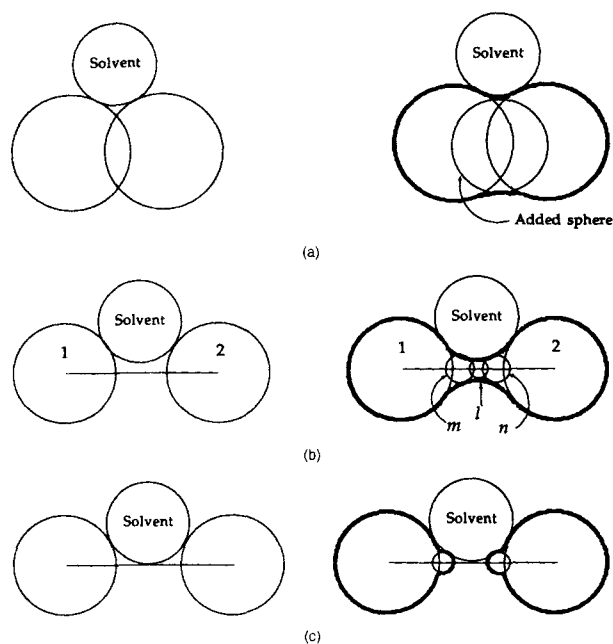
In cases *A* and *B*, the coordinate of the center ( $\alpha_{\text{add}}$ ,  $\alpha = x, y, z$ ) and the radius ( $R_{\text{add}}$ ) of an added sphere are

$$\alpha_{\text{add}} = \frac{1}{2}(\alpha_1 + \alpha_2) - \frac{R_1 - R_2}{2d_{12}}(\alpha_1 - \alpha_2) \quad (1)$$

$$R_{\text{add}} + R_s = \left[ (R_1 + R_s)^2 + \frac{d_{12}^2 + R_1^2 - R_2^2}{2} \right]^{1/2}$$



**FIGURE 1.** Definition of the different kinds of molecular surfaces: (a) van der Waals surface, (b) accessible surface, (c) solvent excluding surface (reproduced from ref. 16).



**FIGURE 2.** Generation of added spheres to approximate the molecular surface.

$$\times \left( \frac{d_{12} + R_1 - R_2}{2} - \frac{(R_1 + R_S)^2 + d_{12}^2 - (R_2 + R_S)^2}{d_{12}} \right)^{1/2} \quad (2)$$

while in the case C they are

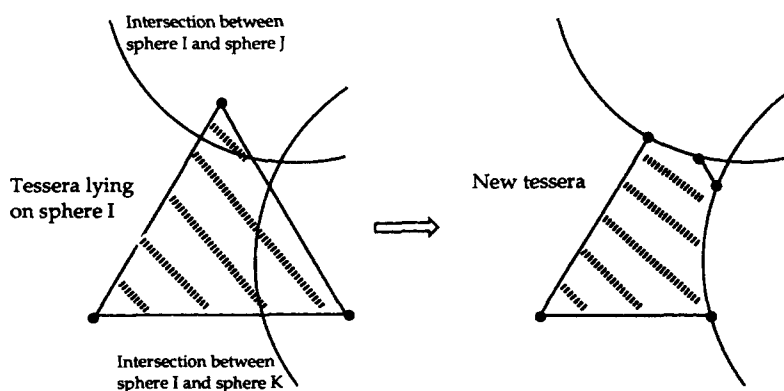
$$\alpha_{\text{add}} = \alpha_1 - \frac{R_1}{d_{12}}(\alpha_1 - \alpha_2) \quad (3)$$

$$R_{\text{add}} + R_S = \left[ (R_1 + R_S)^2 + R_1^2 - R_1 \times \frac{(R_1 + R_S)^2 + d_{12}^2 - (R_2 + R_S)^2}{d_{12}} \right]^{1/2} \quad (4)$$

where index 1 and 2 refer to the couple of the existing spheres that generate the new one,  $d_{12}$  is the distance between their centers, and  $R_S$  is the radius of a solvent molecule (represented as a hard sphere). Sometimes an added sphere generates other added spheres so that a chain of such spheres is formed. For example, in Figure 2 (case B) the atomic spheres 1 and 2 generate the added sphere marked with  $l$ ; then the spheres 1 and  $l$  generate the added sphere  $m$ , and the spheres 2 and  $l$  generate  $n$ . Note that in the case C there is an asymmetry between the generating spheres: In eqs. (3) and (4) the label 1 refers to the sphere intersecting the added sphere.

The cavity is then subdivided into triangular tesserae, corresponding to the projections on the surface of the faces of a pentakis dodecahedron inscribed in each sphere. Tesserae completely buried by some other spheres are discarded, while those cut by intersections with one or more other spheres are replaced by new polygonal tesserae (Fig. 3).

Note that some edges of the new polygonal tesserae are parts of the original edges and lie on great circles, while other edges lie on the intersection circles between the spheres. The position of the new vertices, formed by an intersection circle and an original edge, is determined with a numerical procedure.



**FIGURE 3.** A tessera (on sphere  $I$ ) partially covered by external spheres  $J$  and  $K$  is replaced with a new polygon. The vertices of the old and the new tessera are marked.

In the original version of GEPOL,<sup>4,17</sup> the intersections between spheres were treated by recursively subdividing the cut tesserae in smaller triangles. With this technique, however, we cannot get an analytical expression for the area of the cut tesserae, and the calculation of geometrical derivatives is not possible: Thus the recursive partition technique has been abandoned here.

Before presenting the new formulation, let us fix once and for all the notation for the geometrical quantities to be used hereafter. We shall consider the tessera  $i$ , lying on the sphere  $I$ : The vertices of the tessera are numbered anticlockwise, and edge  $n$  connects vertices  $n$  and  $n + 1$ . Each edge has a reference center (i.e., the center of the arc to which the edge belongs). If the edge is part of a great circle, its reference center coincides with the center of  $I$ ; if it lies on an intersection between  $I$  and another sphere, its reference center is the center of the intersection circle. We shall call (vectors in boldface):

$\mathbf{P}_n$  = position of the vertex  $n$  with respect to the center of  $I$

$\mathbf{C}_n$  = position of the reference center of the edge  $n$  with respect to the origin

$\mathbf{v}_n$  = position of the vertex  $n$  with respect to the reference center of the edge  $n$

$\mathbf{v}_n^*$  = position of the vertex  $n$  with respect to the reference center of the edge  $n - 1$

$\mathbf{T}_n$  = vector pointing from the center of  $I$  to the reference center of the edge  $n$  (nonzero only if  $n$  lies on an intersection circle)

The preceding definitions are visualized in Figure 4. Moreover, the symbol  $\hat{\mathbf{A}}$  will indicate a versor (unit vector):

$$\hat{\mathbf{A}} = \frac{\mathbf{A}}{|\mathbf{A}|}$$

In the present version of GEPOL (hereafter GEPOL-GB), the area  $S$  of the polygonal tessera  $i$  is calculated using Gauss-Bonnet theorem<sup>13</sup>:

$$S_i = R_I^2 \left[ 2\pi + \sum_n^{N_i} \phi_n \cos \theta_n - \sum_n^{N_i} \omega_n \right] \quad (5)$$

where  $R_I$  is the radius of the sphere  $I$ ,  $N_i$  is the number of edges and vertices of the polygon (the first summation being extended to the edges and the second to the vertices),  $\phi_n$  is the angle subtending the edge  $n$  (arc polar length),  $\cos \theta_n$  is its

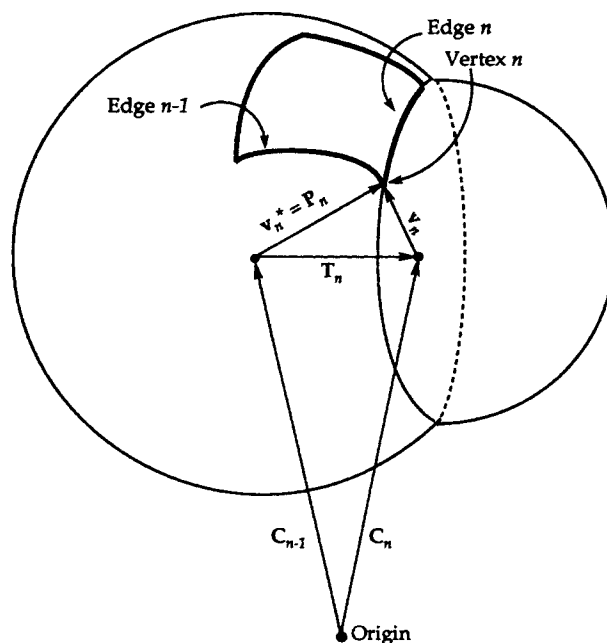


FIGURE 4. Illustration of the geometrical quantities used in the formulas.

polar angle, and  $\omega_n$  is the exterior angle of vertex  $n$ . As shown in Figure 5, with reference to the preceding definitions we have

$$\phi_n = \arccos(\hat{\mathbf{v}}_n \cdot \hat{\mathbf{v}}_{n+1}) \quad (6)$$

$$\cos \theta_n = \hat{\mathbf{v}}_n^* \cdot \hat{\mathbf{T}}_n \quad (7)$$

$$\omega_n = \pi - \arccos(\hat{\mathbf{t}}_{n-1} \cdot \hat{\mathbf{t}}_n) \quad (8)$$

$$\mathbf{t}_{n-1} = \mathbf{v}_n^* \wedge [\mathbf{v}_n^* \wedge \mathbf{v}_{n-1}] \quad (9)$$

$$\mathbf{t}_n = \mathbf{v}_n \wedge [\mathbf{v}_n \wedge \mathbf{v}_{n+1}] \quad (10)$$

Note that  $\cos \theta_n = 0$  if the edge  $n$  lies on a geodesic of  $I$ . In eqs. (6)–(10) we need the geometry of the spheres, the reference centers of the edges, and the positions of the vertices of all the tesserae. These quantities are calculated and stored by GEPOL-GB when it builds the cavity. Definitions (6)–(10), used in eq. (5), permit us to calculate the area of each tessera: The total surface is defined as the sum of all the tesserae. Equation (5) can also be applied to uncut tesserae, although their area is more simply  $1/60$  of the surface of the sphere on which they lie.

The program GEPOL-GB has been tested in a great number of cases, determining both solvent excluding surfaces and accessible surfaces (i.e., with and without added spheres, respectively). The results are in good agreement with the corresponding GEPOL calculations. In Figure 6 we re-

port the solvent excluding surface calculated with both procedures for two separating spheres of radius 2.4 Å. The same model was used in ref. 16 to illustrate the performances of GEPOL. Table I reports the solvent excluding and accessible surfaces for some molecules of increasing complexity calculated with GEPOL and GEPOL-GB procedures.

### Derivatives of Tesseract Area

We are looking for the derivative of  $S_i$  (area of the tessera  $i$ , belonging to the sphere  $I$ ) with respect to the coordinate  $\alpha$  of the sphere  $J$  ( $\alpha = x, y, z$ ):  $dS_i/d\alpha_j$ .  $S_i$  depends on the coordinates of the center (C) and the radius (R) of  $I$  and of all the spheres  $K \neq I$  that cut  $i$  (Fig. 7):

$$S_i = S_i(R_I, C_I\{R_K\}, \{C_K\}) \quad (11)$$

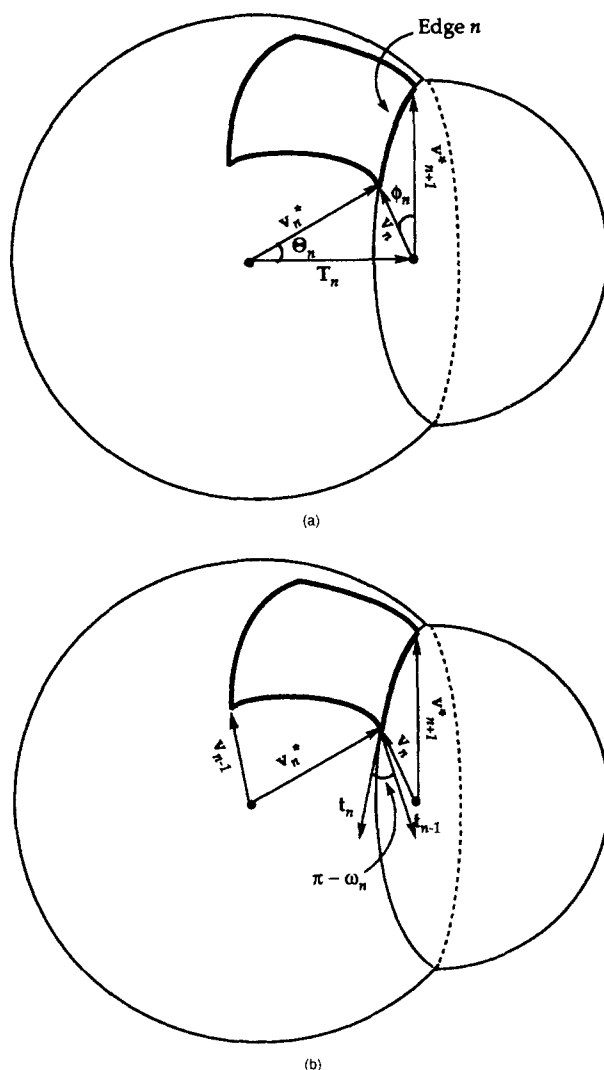
Thus

$$\begin{aligned} \frac{dS_i}{d\alpha_j} = & \frac{\partial S_i}{\partial R_I} \frac{\partial R_I}{\partial \alpha_j} + \sum_{\beta} \left( \frac{\partial S_i}{\partial \beta_I} \frac{\partial \beta_I}{\partial \alpha_j} \right) \\ & + \sum_K \left[ \frac{\partial S_i}{\partial R_K} \frac{\partial R_K}{\partial \alpha_j} + \sum_{\beta} \left( \frac{\partial S_i}{\partial \beta_K} \frac{\partial \beta_K}{\partial \alpha_j} \right) \right] \end{aligned} \quad (12)$$

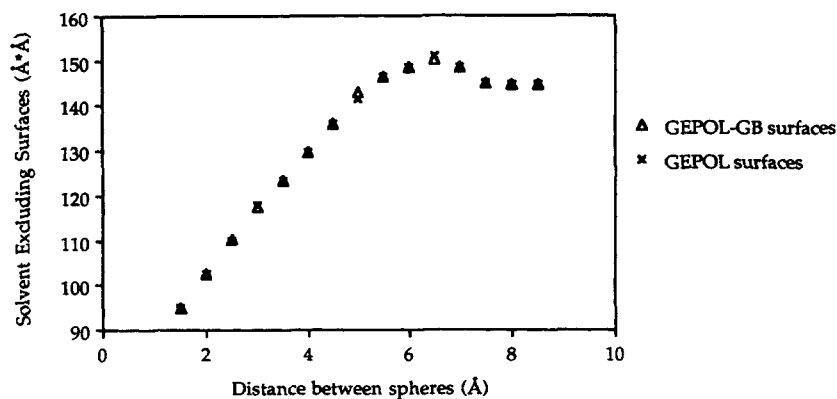
with  $\beta = x, y, z$ .

We want to express eq. (12) in terms of the derivatives of  $S_i$  with respect to the coordinates and the radius of the cutting spheres only. Let us note that

$$\frac{\partial S_i}{\partial \alpha_I} = - \sum_K \frac{\partial S_i}{\partial \alpha_K} \quad (13)$$



**FIGURE 5.** (a) Definition of the arc polar length,  $\phi_n$ , and the polar angle,  $\theta_n$ . (b) Definition of the complementary of the exterior angle,  $\pi - \omega_n$ .



**FIGURE 6.** Solvent excluding surface calculated with GEPOL and GEPOL-GB procedures for two separating spheres of radius 2.4 Å.

**TABLE I.**  
**Solvent Excluding and Accessible Surfaces Calculated with GEPOL and GEPOL-GB Procedures.<sup>a</sup>**

Molecule	Solvent excluding surface (Å <sup>2</sup> )		Accessible surface (Å <sup>2</sup> )	
	GEPOL	GEPOL-GB	GEPOL	GEPOL-GB
H <sub>2</sub> O <sup>b</sup>	35.524	35.716	115.541	115.562
CH <sub>3</sub> CH <sub>2</sub> CH <sub>3</sub> <sup>c</sup>	88.699	89.617	205.913	206.064
CH <sub>3</sub> CO...H <sub>2</sub> O <sup>d</sup>	106.407	107.115	285.330	286.351
Cyclohexane <sup>e</sup>	129.201	130.180	267.056	268.831

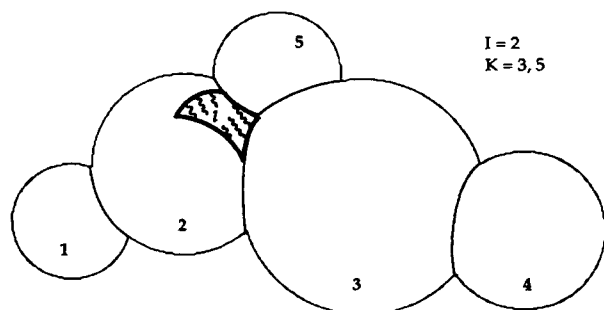
<sup>a</sup> In every case the solvent is a sphere of radius  $R_s = 1.385$  Å (corresponding to a water molecule).

<sup>b</sup> ROH = 0.943 Å,  $\theta = 105.9^\circ$ .

<sup>c</sup> RCH = 1.09 Å, RCC = 1.54 Å,  $\theta_{\text{tetrahedral}} = 109.5^\circ$ .

<sup>d</sup> RCO = 1.24 Å, RCH, RCC, and  $\theta$  as in point (c): The distance between the oxygen of acetaldehyde and the hydrogen of water is 4.5 Å, such that the two molecules are embedded in two distinct cavities (case C of Fig. 2).

<sup>e</sup> MMX optimized geometry.

**FIGURE 7.** Example of tessera cut by two external spheres.

since a small displacement of the sphere  $I$  has the same effect on  $S_i$  as the opposite displacement of all the intersecting spheres; moreover

$$\frac{\partial S_i}{\partial R_I} = \frac{2S_i}{R_I} - \sum_K \left[ \frac{R_K}{R_I} \frac{\partial S_i}{\partial R_K} + \sum_\beta \left( \frac{\beta_K - \beta_I}{R_I} \frac{\partial S_i}{\partial \beta_K} \right) \right] \quad (14)$$

The derivation of eq. (14) is given in the Appendix.

For the sake of simplicity, we shall distinguish between the effects that the change of  $\alpha_j$  has directly on  $S_i$  and the effects mediated by the chains of added spheres that may connect  $S_i$  and  $J$ . The total derivative will result from the sum of these two effects.

### DIRECT EFFECTS

Without reference to added spheres, one has

$$\frac{\partial R_L}{\partial \alpha_J} = 0 \quad \forall L; \quad \frac{\partial \beta_L}{\partial \alpha_J} = \delta_{\alpha\beta} \delta_{LJ} \quad (15)$$

where  $\delta$  indicates the Kronecker function and  $L$  is any sphere. Thus

$$\frac{dS_i}{d\alpha_J} = \begin{cases} \frac{\partial S_i}{\partial \alpha_J} & \text{if } I \neq J \\ - \sum_K \frac{\partial S_i}{\partial \alpha_K} & \text{if } I = J \end{cases} \quad (16)$$

### MEDIATED EFFECTS

For each added sphere  $L$ , one can draw a genealogic tree indicating at the first branching the two spheres that generate  $L$  [through eqs. (1)–(4)]; then, if some of the generating spheres are in turn an added sphere, its parents are placed at the next branching, and so on. The procedure stops when all the ramifications have reached atomic spheres (not generated by any other sphere). We have not considered the case that  $J$  is an added sphere itself, because one is interested in finding the derivatives with respect to the coordinates of an atom of the solute.

If the genealogic tree of  $L$  contains  $J$  at least once,  $L$  and  $J$  are connected and the displacement of  $J$  will influence the position and the size of  $L$ . In this case, recalling eqs. (13) and (14), eq. (12)

reduces to

$$\begin{aligned} \frac{dS_i}{d\alpha_j} = & \frac{\partial R_l}{\partial \alpha_j} \left[ \frac{2S_i}{R_l} - \sum_K \left( \frac{R_K}{R_l} \frac{\partial S_i}{\partial R_K} \right. \right. \\ & \left. \left. + \sum_\beta \frac{\beta_K - \beta_l}{R_l} \frac{\partial S_i}{\partial \beta_K} \right) \right] \\ & - \sum_\beta \left( \frac{\partial \beta_l}{\partial \alpha_j} \sum_K \frac{\partial S_i}{\partial \beta_K} \right) \\ & + \sum_K \left( \frac{\partial R_K}{\partial \alpha_j} \frac{\partial S_i}{\partial R_K} + \sum_\beta \frac{\partial \beta_K}{\partial \alpha_j} \frac{\partial S_i}{\partial \beta_K} \right) \quad (17) \end{aligned}$$

Remember that

$$\frac{\partial R_L}{\partial \alpha_j} \neq 0 \quad \text{and} \quad \frac{\partial \beta_L}{\partial \alpha_j} \neq 0$$

only if  $L$  is an added sphere connected to  $J$ . Note that if the tessera  $i$  is not cut by any sphere  $K$ , the only nonzero contribution to eq. (17) is the first term in the first parenthesis (provided that  $I$  is an added sphere connected to  $J$ ).  $J$  can appear more than once in the genealogic tree of  $L$ : In every case all the chains of added spheres connecting  $J$  and  $L$  are considered, and the results for each chain are summed.

The terms  $\partial R_L / \partial \alpha$ , and  $\partial \beta_L / \partial \alpha_j$ , ( $L = I, K$ ), appearing in eq. (17), are composed derivatives if the connection between  $J$  and  $L$  is mediated by some other added sphere. However, it is easy to show that they are simple combinations of the following derivatives [cases  $A$  and  $B$ ; see eqs. (1) and (2)]:

$$\begin{aligned} \frac{\partial R_{\text{add}}}{\partial R_1} = & \frac{1}{4d_{12}R_{\text{add}}^*} [3R_1^*(d_{12} - R_1^*) \\ & - R_2^*(d_{12} - R_2^*) + 2R_1^*R_2^*] \quad (18) \end{aligned}$$

$$\begin{aligned} \frac{\partial R_{\text{add}}}{\partial \alpha_1} = & \frac{\alpha_1 - \alpha_2}{4d_{12}^3R_{\text{add}}^*} \\ & \times [-d_{12}^3 + (R_1^* + R_2^*)(R_1^* - R_2^*)^2] \quad (19) \end{aligned}$$

$$\frac{\partial \alpha_{\text{add}}}{\partial R_1} = -\frac{\alpha_1 - \alpha_2}{2d_{12}} \quad (20)$$

$$\begin{aligned} \frac{\partial \beta_{\text{add}}}{\partial \alpha_1} = & \left( \frac{1}{2} - \frac{R_1 - R_2}{2d_{12}} \right) \delta_{\alpha\beta} \\ & + \frac{(R_1 - R_2)(\alpha_1 - \alpha_2)(\beta_1 - \beta_2)}{2d_{12}^3} \quad (21) \end{aligned}$$

or of the following ones [case  $C$ ; see eqs. (3) and (4)]:

$$\begin{aligned} \frac{\partial R_{\text{add}}}{\partial R_1} = & \frac{1}{2d_{12}R_{\text{add}}^*} [2d_{12}R_1^* + 2d_{12}R_1 \\ & - 2R_1R_1^* - R_1^{*2} - R_2^{*2} + d_{12}^2] \quad (22) \end{aligned}$$

$$\frac{\partial R_{\text{add}}}{\partial R_2} = \frac{R_1R_2^*}{d_{12}R_{\text{add}}^2} \quad (23)$$

$$\frac{\partial R_{\text{add}}}{\partial \alpha_1} = \frac{R_1(\alpha_1 - \alpha_2)(-d_{12}^2 + R_1^{*2} - R_2^{*2})}{2d_{12}^3R_{\text{add}}^*} \quad (24)$$

$$\frac{\partial \alpha_{\text{add}}}{\partial R_1} = -\frac{\alpha_1 - \alpha_2}{d_{12}} \quad (25)$$

$$\frac{\partial \alpha_{\text{add}}}{\partial R_2} = 0 \quad (26)$$

$$\begin{aligned} \frac{\partial \beta_{\text{add}}}{\partial \alpha_1} = & \left( 1 - \frac{R_1}{d_{12}} \right) \delta_{\alpha\beta} + \frac{R_1(\alpha_1 - \alpha_2)(\beta_1 - \beta_2)}{d_{12}^3} \quad (27) \end{aligned}$$

$$\frac{\partial \beta_{\text{add}}}{\partial \alpha_2} = \frac{R_1}{d_{12}} \delta_{\alpha\beta} - \frac{R_1(\alpha_1 - \alpha_2)(\beta_1 - \beta_2)}{d_{12}^3} \quad (28)$$

where  $R^*$  indicates the radius augmented by the solvent radius  $R_s$ , and the other quantities have been illustrated when dealing with eqs. (1)–(4). Remember the meaning of labels 1 and 2 when the added sphere is of kind  $C$ ; eq. (24) holds also for the derivative with respect to  $\alpha_2$ . At this point, derivatives (16) and (17) depend only on  $\partial S_i / \partial R_K$  and  $\partial S_i / \partial \beta_K$  ( $\beta = x, y, z$ ), where  $K$  is a sphere that cuts  $i$ , thus forming one of its edges. For brevity, let us indicate both  $R_K$  and  $\beta_K$  with  $\xi$ . Differentiation of eq. (5) with respect to  $\xi$  gives

$$\begin{aligned} \frac{\partial S_i}{\partial \xi} = & R_l^2 \left[ \sum_n^{\text{edges}} \frac{\partial \phi_n}{\partial \xi} \cos \theta_n \right. \\ & \left. + \sum_n^{\text{edges}} \phi_n \frac{\partial \cos \theta_n}{\partial \xi} - \sum_n^{\text{vertices}} \frac{\partial \omega_n}{\partial \xi} \right] \quad (29) \end{aligned}$$

If  $\mathbf{a}$  and  $\mathbf{b}$  are any vectors and  $\Phi$  is the angle between them, two useful relations hold:

$$\frac{\partial \Phi}{\partial \xi} = -\frac{1}{\sin \Phi} \frac{\partial \cos \Phi}{\partial \xi} \quad (30)$$

$$\begin{aligned} \frac{\partial \cos \Phi}{\partial \xi} &= \frac{\partial}{\partial \xi} \frac{\mathbf{a} \cdot \mathbf{b}}{|\mathbf{a}| |\mathbf{b}|} \\ &= \frac{1}{|\mathbf{a}| |\mathbf{b}|} \left[ \left( \mathbf{a} - \cos \Phi \frac{|\mathbf{a}|}{|\mathbf{b}|} \mathbf{b} \right) \cdot \frac{\partial \mathbf{b}}{\partial \xi} \right. \\ &\quad \left. + \left( \mathbf{b} - \cos \Phi \frac{|\mathbf{b}|}{|\mathbf{a}|} \mathbf{a} \right) \cdot \frac{\partial \mathbf{a}}{\partial \xi} \right] \quad (31) \end{aligned}$$

We shall express all the derivatives in eq. (29) in terms of  $\partial \mathbf{P}_n / \partial \xi$  only.

#### DERIVATIVE OF THE ARC POLAR LENGTH $\phi_n$

From Figures 4 and 5a it is evident that

$$\mathbf{v}_n = \mathbf{P}_n - \mathbf{T}_n; \quad \mathbf{v}_{n+1}^* = \mathbf{P}_{n+1} - \mathbf{T}_n \quad (32)$$

Differentiating eq. (6) and using eqs. (30), (31), and (32) we have

$$\begin{aligned} \frac{\partial \phi_n}{\partial \xi} &= \frac{-1}{\sin \phi_n R_C^2} \\ &\times \left[ (\mathbf{v}_n - \cos \phi_n \mathbf{v}_{n+1}^*) \cdot \left( \frac{\partial \mathbf{P}_{n+1}}{\partial \xi} - \frac{\partial \mathbf{T}_n}{\partial \xi} \right) \right. \\ &\quad \left. + (\mathbf{v}_{n+1}^* - \cos \phi_n \mathbf{v}_n) \cdot \left( \frac{\partial \mathbf{P}_n}{\partial \xi} - \frac{\partial \mathbf{T}_n}{\partial \xi} \right) \right] \quad (33) \end{aligned}$$

where  $R_C$  is the radius of the intersection circle where the edge  $n$  lies.

If  $\mathbf{D}_{IK}$  is the vector pointing from the center of  $I$  to the center of  $K$ ,  $\mathbf{T}_n$  is directed along  $\mathbf{D}_{IK}$ :

$$\mathbf{T}_n = \frac{R_I^2 - R_K^2 + |\mathbf{D}_{IK}|^2}{2 |\mathbf{D}_{IK}|} \hat{\mathbf{D}}_{IK} = f_{IK} \hat{\mathbf{D}}_{IK} \quad (34)$$

Hence, if  $\xi = R_K$ ,

$$\frac{\partial \mathbf{T}_n}{\partial R_K} = - \frac{R_K}{|\mathbf{D}_{IK}|} \hat{\mathbf{D}}_{IK} \quad (35)$$

while if  $\xi = \beta_K$ ,

$$\frac{\partial \mathbf{T}_n}{\partial \beta_K} = \frac{f_{IK}}{|\mathbf{D}_{IK}|} \hat{\beta} - \frac{R_I^2 - R_K^2}{|\mathbf{D}_{IK}|^4} (\mathbf{D}_{IK})_\beta \mathbf{D}_{IK} \quad (36)$$

where  $(\mathbf{D}_{IK})_\beta$  is the  $\beta$  component of the vector  $\mathbf{D}_{IK}$ , and  $\hat{\beta}$  is the versor directed along the axis  $\beta$ .

In eq. (33) the derivative  $\partial \mathbf{T}_n / \partial \xi$  has to be multiplied by  $\mathbf{v}_n$  and  $\mathbf{v}_{n+1}^*$ . Because the vector  $\mathbf{D}_{IK}$  is normal to the intersection circle (and thus to  $\mathbf{v}_n$  and  $\mathbf{v}_{n+1}^*$ ), the second term on the right-hand side

of eq. (36) does not contribute to the dot product, and one can discard it. Equations (35) and (36), inserted in eq. (33), leave only the terms  $\partial \mathbf{P}_n / \partial \xi$  and  $\partial \mathbf{P}_{n+1} / \partial \xi$  to be calculated.

#### DERIVATIVE OF THE COSINE OF THE POLAR ANGLE $\cos \theta_n$

Recalling eq. (7) and applying eq. (31),

$$\begin{aligned} \frac{\partial \cos \theta_n}{\partial \xi} &= \frac{1}{R_I |\mathbf{D}_{IK}|} \\ &\times \left[ \left( \mathbf{P}_n - \cos \theta_n \frac{R_I}{|\mathbf{D}_{IK}|} \mathbf{D}_{IK} \right) \cdot \frac{\partial \mathbf{D}_{IK}}{\partial \xi} \right. \\ &\quad \left. + \left( \mathbf{D}_{IK} - \cos \theta_n \frac{|\mathbf{D}_{IK}|}{R_I} \mathbf{P}_n \right) \cdot \frac{\partial \mathbf{P}_n}{\partial \xi} \right] \quad (37) \end{aligned}$$

where we have used the relation  $\hat{\mathbf{P}}_n \cdot \hat{\mathbf{T}}_n = \hat{\mathbf{P}}_n \cdot \hat{\mathbf{D}}_{IK}$ . As shown next,  $\mathbf{P}_n \cdot \partial \mathbf{P}_n / \partial \xi = 0$ ; moreover, if  $\xi = R_K$ , it is clear that  $\partial \mathbf{D}_{IK} / \partial \xi = 0$ . Thus

$$\begin{aligned} \frac{\partial \cos \theta_n}{\partial \xi} &= \begin{cases} \frac{1}{R_I |\mathbf{D}_{IK}|} \mathbf{D}_{IK} \cdot \frac{\partial \mathbf{P}_n}{\partial R_K} & \text{if } \xi = R_K \\ \frac{1}{R_I |\mathbf{D}_{IK}|} \left[ (\mathbf{P}_n)_\beta - \frac{R_I}{|\mathbf{D}_{IK}|} \right. \\ \quad \left. \times \cos \theta_n (\mathbf{D}_{IK})_\beta + \mathbf{D}_{IK} \cdot \frac{\partial \mathbf{P}_n}{\partial \beta_K} \right] & \text{if } \xi = \beta_K \end{cases} \quad (38) \end{aligned}$$

where, as usual,  $(\mathbf{P}_n)_\beta$  indicates the  $\beta$  component of the vector  $\mathbf{P}_n$ .

#### DERIVATIVE OF THE EXTERIOR ANGLE $\omega_n$

From eq. (8) one has

$$\begin{aligned} \frac{\partial \omega_n}{\partial \xi} &= \frac{1}{\sin \omega_n |t_n| |t_{n-1}|} \\ &\times \left[ \left( \mathbf{t}_n - \cos \omega_n \frac{|t_n|}{|t_{n-1}|} \mathbf{t}_{n-1} \right) \cdot \frac{\partial \mathbf{t}_{n-1}}{\partial \xi} \right. \\ &\quad \left. + \left( \mathbf{t}_{n-1} - \cos \omega_n \frac{|t_{n-1}|}{|t_n|} \mathbf{t}_n \right) \cdot \frac{\partial \mathbf{t}_n}{\partial \xi} \right] \quad (39) \end{aligned}$$



with

$$\begin{aligned}\frac{\partial \mathbf{t}_n}{\partial \xi} &= \frac{\partial \mathbf{v}_n}{\partial \xi} \wedge (\mathbf{v}_n \wedge \mathbf{v}_{n+1}^*) + \mathbf{v}_n \\ &\quad \wedge \left( \frac{\partial \mathbf{v}_n}{\partial \xi} \wedge \mathbf{v}_{n+1}^* \right) + \mathbf{v}_n \wedge \left( \mathbf{v}_n \wedge \frac{\partial \mathbf{v}_{n+1}^*}{\partial \xi} \right) \\ \frac{\partial \mathbf{t}_{n-1}}{\partial \xi} &= \frac{\partial \mathbf{v}_n^*}{\partial \xi} \wedge (\mathbf{v}_n^* \wedge \mathbf{v}_{n-1}) + \mathbf{v}_n^* \\ &\quad \wedge \left( \frac{\partial \mathbf{v}_n^*}{\partial \xi} \wedge \mathbf{v}_{n-1} \right) + \mathbf{v}_n^* \wedge \left( \mathbf{v}_n^* \wedge \frac{\partial \mathbf{v}_{n-1}}{\partial \xi} \right)\end{aligned}$$

If the edge  $n$  is (a part of) one of the original edges of the tessera (thus lying on a geodesic of  $I$ ), one has

$$\frac{\partial \mathbf{v}_n}{\partial \xi} = \frac{\partial \mathbf{P}_n}{\partial \xi} \quad (40)$$

while if the edge  $n$  lies on an intersection circle, one has

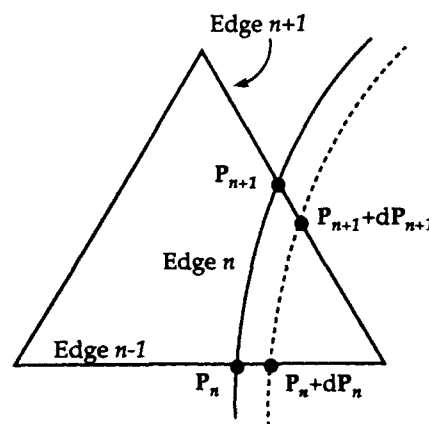
$$\mathbf{v}_n = \mathbf{P}_n - \mathbf{T}_n \quad (41)$$

Then, from eqs. (35) and (36),

$$\begin{aligned}\frac{\partial \mathbf{v}_n}{\partial \xi} &= \begin{cases} \frac{\partial \mathbf{P}_n}{\partial \xi} + \frac{R_K}{|D_{IK}|} \hat{\mathbf{D}}_{IK} & \text{if } \xi = R_K \\ \frac{\partial \mathbf{P}_n}{\partial \xi} - \frac{f_{IK}}{|D_{IK}|} \hat{\beta} \\ \quad + \frac{R_I^2 - R_K^2}{|D_{IK}|^4} (\mathbf{D}_{IK})_\beta \mathbf{D}_{IK} & \text{if } \xi = \beta_K \end{cases} \quad (42)\end{aligned}$$

### DERIVATIVE OF THE VERTEX POSITION $\mathbf{P}_n$

Expressions (33), (38), (40), and (42) depend only on  $\partial \mathbf{P}_n / \partial \xi$  and  $\partial \mathbf{P}_{n+1} / \partial \xi$ . To calculate these derivatives, let us consider what happens to a cut tessera when one of the coordinates of the center or the radius of the cutting sphere ( $K$ ) changes by  $d\xi$ . If  $\mathbf{P}_n$  and  $\mathbf{P}_{n+1}$  are on the intersection circle, they change by  $d\mathbf{P}_n$  and  $d\mathbf{P}_{n+1}$ , respectively. As shown in Figure 8, the new vertices  $\mathbf{P}_n + d\mathbf{P}_n$  and  $\mathbf{P}_{n+1} + d\mathbf{P}_{n+1}$  lie on edges  $n-1$  and  $n+1$ , re-



**FIGURE 8.** What happens to a cut tessera when the center or the radius of the cutting sphere moves.

spectively. This condition may be expressed as

$$d\mathbf{P}_n = A \hat{\mathbf{t}}_{n-1}; \quad d\mathbf{P}_{n+1} = B \hat{\mathbf{t}}_{n+1} \quad (43)$$

where  $A$  and  $B$  are scalar numbers and  $\hat{\mathbf{t}}_{n-1}$  and  $\hat{\mathbf{t}}_{n+1}$  are versors tangent to sphere  $I$ , directed along the edges  $n-1$  and  $n+1$ , respectively. The definitions of these tangent versors are analogous to those given in eqs. (9) and (10).

Because  $\mathbf{P}_n + d\mathbf{P}_n$  must be on the surface of the sphere  $K$ , we may write

$$\begin{aligned}[\mathbf{P}_n + d\mathbf{P}_n - \mathbf{D}_{IK}] \cdot [\mathbf{P}_n + d\mathbf{P}_n - \mathbf{D}_{IK}] &= (R_K + dR_K)^2 \quad (44)\end{aligned}$$

if  $\xi = R_K$ , and

$$\begin{aligned}[\mathbf{P}_n + d\mathbf{P}_n - \mathbf{D}_{IK} + d\mathbf{D}_{IK}] \cdot [\mathbf{P}_n + d\mathbf{P}_n - \mathbf{D}_{IK} + d\mathbf{D}_{IK}] &= R_K^2 \quad (45)\end{aligned}$$

if  $\xi = \beta_K$ . Recalling that  $[\mathbf{P}_n - \mathbf{D}_{IK}]^2 = R_K^2$ , and discarding the second-order terms, one obtains from eq. (44)

$$\begin{aligned}d\mathbf{P}_n \cdot [\mathbf{P}_n - \mathbf{D}_{IK}] &= A \hat{\mathbf{t}}_{n-1} \cdot [\mathbf{P}_n - \mathbf{D}_{IK}] = R_K dR_K \\ \frac{\partial \mathbf{P}_n}{\partial R_K} &= \frac{R_K}{\hat{\mathbf{t}}_{n-1} \cdot [\mathbf{P}_n - \mathbf{D}_{IK}]} \hat{\mathbf{t}}_{n-1} \quad (46)\end{aligned}$$

and, from eq. (45),

$$\begin{aligned}d\mathbf{P}_n \cdot [\mathbf{P}_n - \mathbf{D}_{IK}] &= A \hat{\mathbf{t}}_{n-1} \cdot [\mathbf{P}_n - \mathbf{D}_{IK}] \\ &= d\mathbf{D}_{IK} \cdot [\mathbf{P}_n - \mathbf{D}_{IK}]\end{aligned}$$

$$\begin{aligned}\frac{\partial \mathbf{P}_n}{\partial \beta_K} &= \frac{\hat{\beta} \cdot [\mathbf{P}_n - \mathbf{D}_{IK}]}{\hat{\mathbf{t}}_{n-1} \cdot [\mathbf{P}_n - \mathbf{D}_{IK}]} \hat{\mathbf{t}}_{n-1} \\ &= \frac{[\mathbf{P}_n - \mathbf{D}_{IK}]_\beta}{\hat{\mathbf{t}}_{n-1} \cdot [\mathbf{P}_n - \mathbf{D}_{IK}]} \hat{\mathbf{t}}_{n-1} \quad (47)\end{aligned}$$

In deriving eq. (47), we have used the relation  $d\mathbf{D}_{IK} = \hat{\beta} d\beta_K$ . The analogous expressions for  $\partial \mathbf{P}_{n+1}/\partial \xi$  are straightforwardly derived. Note that since  $d\mathbf{P}_n$  is tangent to the sphere  $I$ , the product  $\mathbf{P}_n \cdot d\mathbf{P}_n$  vanishes, as previously stated.

## Derivatives of Representative Points and Normal Versors

In the expressions for the analytical solvation energy derivatives, one also needs geometrical derivatives of the position of tesserae representative points and of the versors normal to the cavity surface.

For each tessera GEPOL-GB defines a representative point  $\mathbf{Q}_i$ , at which the polarization charge has to be placed, as the average of tessera vertices:

$$\mathbf{Q}_i = \frac{\sum_n^{N_i} \mathbf{P}_n}{|\sum_n^{N_i} \mathbf{P}_n|} R_I \quad (48)$$

where, as usual,  $R_I$  is the radius of the sphere to which tessera  $i$  belongs. Also in this case, it is convenient to reduce  $d\mathbf{Q}_i/d\alpha_j$  to a combination of derivatives  $\partial \mathbf{Q}_i/\partial \xi_K$ , where  $\xi_K$  indicates one of the center coordinates or the radius of a sphere that cuts the tessera  $i$ .

Equations (12) and (13) still hold, provided that one replaces  $S_i$  with  $\mathbf{Q}_i$ . Equation (14) can also be used, but in this case the dependence of  $\mathbf{Q}_i$  on the scaling parameter  $\lambda$  is linear, so that  $\partial \mathbf{Q}_i/\partial \lambda|_{\lambda=1} = \mathbf{Q}$ . Thus, keeping the distinction between direct and mediated effects, one has

$$\frac{d\mathbf{Q}_i}{d\alpha_j} = \begin{cases} \frac{\partial \mathbf{Q}_i}{\partial \alpha_j} & \text{if } I \neq J \\ -\sum_K \frac{\partial \mathbf{Q}_i}{\partial \alpha_K} & \text{if } I = J \end{cases} \quad (49)$$

for direct effects, and

$$\begin{aligned}\frac{d\mathbf{Q}_i}{d\alpha_j} &= \frac{\partial R_I}{\partial \alpha_j} \left[ \frac{\mathbf{Q}_i}{R_I} - \sum_K \left( \frac{R_K}{R_I} \frac{\partial \mathbf{Q}_i}{\partial R_K} \right. \right. \\ &\quad \left. \left. + \sum_\beta \frac{\beta_K - \beta_I}{R_I} \frac{\partial \mathbf{Q}_i}{\partial \beta_K} \right) \right]\end{aligned}$$

$$\begin{aligned}& - \sum_\beta \left( \frac{\partial \beta_I}{\partial \alpha_j} \sum_K \frac{\partial \mathbf{Q}_i}{\partial \beta_K} \right) \\ & + \sum_K \left( \frac{\partial R_K}{\partial \alpha_j} \frac{\partial \mathbf{Q}_i}{\partial R_K} + \sum_\beta \frac{\partial \beta_K}{\partial \alpha_j} \frac{\partial \mathbf{Q}_i}{\partial \beta_K} \right) \quad (50)\end{aligned}$$

for mediated effects.

Equations (18)–(28) can be used without changes to calculate some of the derivatives in eq. (50); as in the case of area derivatives, the only terms to be found are now  $\partial \mathbf{Q}_i/\partial R_K$ ,  $\partial \mathbf{Q}_i/\partial \beta_K$  ( $\beta = x, y, z$ ). Since for any vector  $\mathbf{A}$

$$\frac{\partial |\mathbf{A}|}{\partial \xi} = \frac{1}{|\mathbf{A}|} \mathbf{A} \cdot \frac{\partial \mathbf{A}}{\partial \xi}$$

from eq. (48) one sees that

$$\begin{aligned}\frac{\partial \mathbf{Q}_i}{\partial \xi} &= \frac{R_I}{|\sum_n^{N_i} \mathbf{P}_n|} \sum_n \frac{\partial \mathbf{P}_n}{\partial \xi} \\ &- \frac{\mathbf{Q}_i}{R_I |\sum_n^{N_i} \mathbf{P}_n|} \left( \mathbf{Q}_i \cdot \sum_n \frac{\partial \mathbf{P}_n}{\partial \xi} \right) \quad (51)\end{aligned}$$

Remember that the term  $\partial R_I/\partial \xi$  has been considered in eq. (50); the derivatives of tessera vertex positions, appearing in eq. (51), have already been found.

The versor  $\hat{\mathbf{n}}_i$ , perpendicular to the cavity surface in point  $\mathbf{Q}_i$  and pointing outward, is defined as

$$\hat{\mathbf{n}}_i = \hat{\mathbf{Q}}_i = \frac{\mathbf{Q}_i}{|\mathbf{Q}_i|} \quad (52)$$

Its derivative with respect to  $\xi$  is simply

$$\frac{\partial \hat{\mathbf{n}}_i}{\partial \xi} = \frac{1}{R_I} \frac{\partial \mathbf{Q}_i}{\partial \xi} \quad (53)$$

To obtain the derivatives of  $\hat{\mathbf{n}}_i$  with respect to the coordinates of the solute atoms, one can resort to eqs. (49) and (50), replacing  $\mathbf{Q}_i$  with  $\hat{\mathbf{n}}_i$ : The only difference is that  $\hat{\mathbf{n}}_i$  does not depend on the scaling of the sphere  $I$ , so the first term in the first parenthesis of eq. (50) (namely,  $\mathbf{Q}_i/R_I$ ) must be discarded.

Remember that all the position vectors defined earlier (for vertices and representative points) are referred to the center of the sphere where the tessera  $i$  lies. It is an easy matter to find the derivatives of the corresponding vectors referred to the origin.

## Derivatives of Solute–Solvent Dispersion–Repulsion Energy

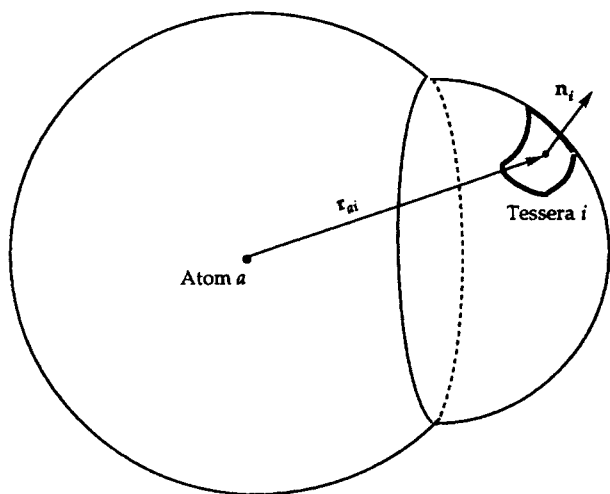
PCM calculates the dispersion–repulsion contribution to the solute–solvent interaction by means of an atom–atom potential method.<sup>21</sup> Caillet and Claverie<sup>21,22</sup> defined some atom–atom potentials that can be used to account for interactions between each couple of solute and solvent atoms. Floris and Tomasi<sup>23,24</sup> have proposed a procedure, currently implemented in PCM, to calculate the dispersion–repulsion interaction by means of a surface integral, transformed into a sum of terms defined on each tessera of the cavity surface. In this description the dispersion (repulsion) contribution to the solute–solvent free energy is

$$G^{\text{disp(rep)}} = \sum_a \sum_s \rho_s \sum_i S_i A^{\text{disp(rep)}} \mathbf{r}_{ai} \cdot \hat{\mathbf{n}}_i \quad (54)$$

where the indexes  $a$  and  $s$  run over the atoms of solute and solvent molecules, respectively,  $\rho_s$  is the number density of the solvent molecules,  $i$  indicates the tesserae on the cavity surface,  $S_i$  is the area of the tessera  $i$ ,  $\hat{\mathbf{n}}_i$  is the versor normal to the cavity in the representative point of  $i$ , and the vector  $\mathbf{r}_{ai}$  points from atom  $a$  to the representative point of  $i$  (Fig. 9).

If  $\mathbf{r}_{as}$  is the vector from atom  $a$  to atom  $s$  and the dispersion and the repulsion interactions between  $a$  and  $s$  are described as

$$V^{\text{disp}}(\mathbf{r}_{as}) = -d_{as} |\mathbf{r}_{as}|^{-6}$$



**FIGURE 9.** Illustration of the geometrical quantities appearing in eq. (54).

and

$$V^{\text{rep}}(\mathbf{r}_{as}) = B_{as} \exp(-\gamma_{as} |\mathbf{r}_{as}|)$$

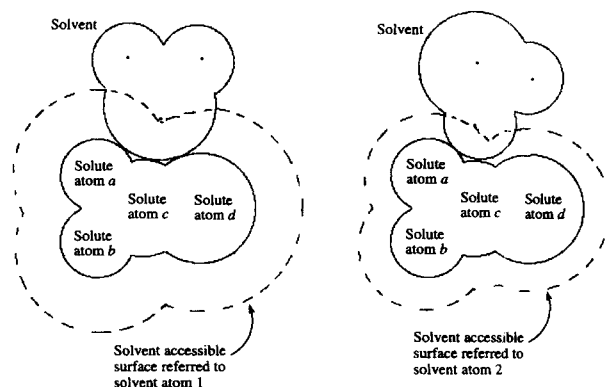
respectively, the terms  $A^{\text{disp}}$  and  $A^{\text{rep}}$  in eq. (54) are

$$A^{\text{disp}} = -\frac{1}{3} d_{as} |\mathbf{r}_{ai}|^{-6} \quad (55)$$

$$A^{\text{rep}} = B_{as} \exp(-\gamma_{as} |\mathbf{r}_{ai}|) \times \left[ \frac{1}{\gamma_{as} |\mathbf{r}_{ai}|} + \frac{2}{(\gamma_{as} |\mathbf{r}_{ai}|)^2} + \frac{2}{(\gamma_{as} |\mathbf{r}_{ai}|)^3} \right] \quad (56)$$

and  $d_{as}$ ,  $B_{as}$ , any  $\gamma_{as}$  can be calculated from Caillet-Claverie's atomic parameters, tabulated for many elements. [Note that in the Appendix of ref. 24 there are a couple of misprints in the expression of  $A^{\text{rep}}$ : the correct form is that reported in eq. (56).]

As noted earlier, the cavity suitable for the calculation of dispersion–repulsion terms is different from that used for the electrostatic terms. In the case of dispersion–repulsion, in fact, one makes use of atom–atom potentials depending on the distances between the nuclei. It is appropriate, then, to define the cavity as the portion of space from which the nuclei of the solvent atoms are excluded. For each solvent atom one defines a new surface, described (as before) with a set of spheres centered on the solute atoms. In this case, however, the radii of the spheres are augmented by the



**FIGURE 10.** Definition of solvent accessible surfaces referred to solvent atoms. Each surface is described by the center of a spherical solvent atom rolling on the solute.

radius of the solvent atom. These surfaces correspond to the solvent accessible surfaces<sup>16</sup> defined earlier (Figs. 1 and 10). To divide these surfaces in tesserae, one follows the same procedure previously described for the solvent excluding surfaces.

For an accessible surface there is no need to define any added sphere, as in the case of the solvent excluding surface used in the preceding sections. Thus we shall consider only direct effects in calculation of the following derivatives.

The derivatives of  $G^{\text{disp(rep)}}$  with respect to the coordinate  $\alpha$  of the atom  $J$  is

$$\frac{\partial G^{d(r)}}{\partial \alpha_J} = \sum_a \sum_s \rho_s \sum_i \left[ \frac{\partial S_i}{\partial \alpha_J} A^{d(r)} \mathbf{r}_{ai} \cdot \hat{\mathbf{n}}_i + S_i \frac{\partial A^{d(r)}}{\partial \alpha_J} \mathbf{r}_{ai} \cdot \hat{\mathbf{n}}_i + S_i A^{d(r)} \frac{\partial (\mathbf{r}_{ai} \cdot \hat{\mathbf{n}}_i)}{\partial \alpha_J} \right] \quad (57)$$

The term  $\partial S_i / \partial \alpha_J$  has been calculated earlier; the derivatives of  $A^{\text{disp}}$ ,  $A^{\text{rep}}$ , and  $\mathbf{r}^{ai} \cdot \hat{\mathbf{n}}_i$  are, respectively,

$$\frac{\partial A^d}{\partial \alpha_J} = 2 \frac{d_{as}}{|r_{ai}|^7} \frac{\partial |r_{ai}|}{\partial \alpha_J} \quad (58)$$

$$\begin{aligned} \frac{\partial A^r}{\partial \alpha_J} = & - \left[ \gamma_{as} A^r + B_{as} \exp(-\gamma_{as} |r_{ai}|) \right. \\ & \times \left( \frac{1}{\gamma_{as} |r_{ai}|^2} + \frac{4}{\gamma_{as}^2 |r_{ai}|^3} \right. \\ & \left. \left. + \frac{6}{\gamma_{as}^3 |r_{ai}|^4} \right) \right] \frac{\partial |r_{ai}|}{\partial \alpha_J} \quad (59) \end{aligned}$$

$$\frac{\partial (\mathbf{r}_{ai} \cdot \hat{\mathbf{n}}_i)}{\partial \alpha_J} = \frac{\partial \mathbf{r}_{ai}}{\partial \alpha_J} \cdot \hat{\mathbf{n}}_i + \mathbf{r}_{ai} \cdot \frac{\partial \hat{\mathbf{n}}_i}{\partial \alpha_J} \quad (60)$$

The term  $\partial \hat{\mathbf{n}}_i / \partial \alpha_J$  has been calculated earlier; the derivative of the norm of  $\mathbf{r}_{ai}$  is

$$\frac{\partial |r_{ai}|}{\partial \alpha_J} = \hat{\mathbf{r}}_{ai} \cdot \frac{\partial \mathbf{r}_{ai}}{\partial \alpha_J} \quad (61)$$

The only quantity to be determined is then  $\partial \mathbf{r}_{ai} / \partial \alpha_J$  which can be easily expressed in terms of the derivatives of the representative point of tessera

$i$  (see Fig. 9):

$$\frac{\partial \mathbf{r}_{ai}}{\partial \alpha_J} = \begin{cases} \frac{\partial \mathbf{Q}_i}{\partial \alpha_J} + \hat{\alpha} & \text{if } i \text{ belongs to the sphere } J \\ & \text{and } a \neq J \\ \frac{\partial \mathbf{Q}_i}{\partial \alpha_J} - \hat{\alpha} & \text{if } i \text{ belongs to the sphere } a \\ & \text{and } a \neq J \\ \frac{\partial \mathbf{Q}_i}{\partial \alpha_J} & \text{otherwise} \end{cases} \quad (62)$$

Here again  $\hat{\alpha}$  is the versor along axis  $\alpha$ .

Formally, calculation of both the derivatives of  $G^{\text{disp(rep)}}$  and the derivatives of Hartree-Fock energy makes use of the same quantities ( $dS_i/d\alpha_J$ ,  $d\hat{\mathbf{n}}_i/d\alpha_J$ ,  $d\mathbf{P}_n/d\alpha_J$ ), calculated in the preceding sections. Remember, however, that the dispersion-repulsion contribution and the internal and electrostatic contribution to the free energy use different definitions of the cavity. Thus, the geometrical derivatives have to be calculated for different cavities.

## Examples of Applications

The preceding algorithms have been implemented in a version of HONDO8,<sup>26</sup> which can routinely calculate the solute-solvent PCM interaction energy and the geometrical derivatives of the solute molecular surface and of the dispersion-repulsion contribution to the interaction energy. Some test calculations have been performed to check the reliability of the method and its computational weight. The solute molecules were  $\text{H}_2\text{O}$ ,  $\text{CH}_3\text{CH}_2\text{CH}_3$ , and  $\text{CH}_3\text{CHO} \cdots \text{H}_2\text{O}$  (see Fig. 11); in every case the solvent was water.

In Tables II through IV we report the calculated analytical derivatives of solvent excluding and accessible surfaces with respect to the solute nuclear coordinates, compared with the corresponding numerical derivatives obtained as the limit of the incremental ratio. To save space, in the case of propane and acetaldehyde-water, only the coordinates with the largest derivatives are listed: The quality of results is well represented by the reported examples. The magnitude of the calculated molecular surface derivatives shows that such derivatives are not negligible and confirms that

**TABLE II.**  
**Analytical Derivatives of Solvent Excluding and Accessible Surface of H<sub>2</sub>O with Respect to Atomic Coordinates, Compared to Numerical Derivatives.**

Atom	Coord.	Derivatives of solvent excluding surface (Å)		Derivatives of accessible surface (Å)	
		Analytical	Numerical	Analytical	Numerical
O	x	−0.0006	−0.0008	0.0	0.0
	y	0.0	0.0002	0.0	0.0
	z	−9.3910	−9.3880	−15.4671	−15.4629
H <sub>1</sub>	x	6.0023	6.0017	12.5702	12.5685
	y	0.0	0.0005	0.0	0.0024
	z	4.6957	4.6955	7.7335	7.7361
H <sub>2</sub>	x	−6.0017	−6.0025	−12.5702	−12.5700
	y	0.0	0.0002	0.0	0.0015
	z	4.6953	4.6959	7.7335	7.7320
Translational invariance <sup>a</sup>	x	0.0000	−0.0016	0.0000	0.0022
	y	0.0000	0.0009	0.0000	0.0039
	z	0.0000	0.0027	0.0000	0.0052

<sup>a</sup> Sum of the derivatives with respect to the same coordinate of all the atoms (corresponding to an overall molecular translation, it should be zero).

**TABLE III.**  
**Analytical Derivatives of Solvent Excluding and Accessible Surface of CH<sub>3</sub>CH<sub>2</sub>CH<sub>3</sub> with Respect to Some Atomic Coordinates, Compared to Numerical Derivatives (see Fig. 11 for the Atomic Labels).**

Atom	Coord.	Derivatives of solvent excluding surface (Å)		Derivatives of accessible surface (Å)	
		Analytical	Numerical	Analytical	Numerical
C <sub>1</sub>	x	1.5604	1.5392	2.7583	2.7474
	y	−4.4033	−4.3996	−2.6240	−3.6316
	z	2.1322	2.1431	1.9463	1.9475
H <sub>1</sub>	x	0.2779	0.2834	1.3737	1.3749
	y	−0.4799	−0.4816	−2.3796	−2.3783
	z	7.4349	7.4256	12.3320	12.3238
C <sub>2</sub>	x	−2.0819	−1.9929	0.3545	0.3550
	y	1.3224	1.3320	1.1234	1.1232
	z	−0.8957	−0.9043	0.2490	0.2494
H <sub>5</sub>	x	7.2549	7.2387	5.8633	5.8672
	y	4.2344	4.2409	7.6030	7.6055
	z	−2.6253	−2.6286	−3.6578	−3.6574
C <sub>3</sub>	x	−4.0412	−4.0436	−3.9968	−4.0013
	y	−1.6379	−1.6367	−0.6985	−0.6821
	z	−2.2614	−2.2590	−2.8130	−2.8090
H <sub>6</sub>	x	−6.5391	−6.5371	−11.8096	−11.8073
	y	2.4536	2.4546	3.3356	3.3359
	z	2.5866	2.5862	2.9959	2.9977
Translational invariance <sup>a</sup>	x	0.0001	0.0009	0.0000	−0.0016
	y	0.0000	0.0012	0.0003	0.0021
	z	−0.0001	−0.0003	0.0000	0.0005

<sup>a</sup> Taking into account nonreported coordinates.

TABLE IV.

Analytical Derivatives of Solvent Excluding and Accessible Surface of  $\text{CH}_3\text{CHO} \cdots \text{H}_2\text{O}$  with Respect to Some Atomic Coordinates, Compared to Numerical Derivatives (see Fig. 11 for the Atomic Labels).

Atom	Coord.	Derivatives of solvent excluding surface (Å)		Derivatives of accessible surface (Å)	
		Analytical	Numerical	Analytical	Numerical
H <sub>1</sub>	x	0.0067	0.0063	-0.0002	0.0001
	y	-6.3533	-6.3540	-11.3500	-11.3492
	z	4.6374	4.6370	4.3597	4.3599
H <sub>2</sub>	x	6.2197	6.2200	10.5467	10.5493
	y	-1.0042	-1.0035	-3.3083	-3.3056
	z	-4.7262	-4.7254	-7.8400	-7.8386
O <sub>1</sub>	x	0.0109	0.0102	-0.0001	-0.0008
	y	0.4408	0.4380	4.2520	4.2490
	z	11.1618	11.1598	2.0360	2.0381
H <sub>4</sub>	x	0.0	0.0008	-0.0004	0.0003
	y	6.7895	6.7900	13.0895	13.0916
	z	-3.9199	-3.9193	-4.8756	-4.8728
H <sub>5</sub>	x	0.0	0.0012	-0.0001	0.0008
	y	0.6362	0.6373	2.2301	2.3176
	z	-10.3003	-10.2984	-1.4773	-1.4738
O <sub>2</sub>	x	0.0	0.0009	0.0	-0.0005
	y	6.6475	6.6479	11.7015	11.7028
	z	4.7417	4.7415	8.3466	8.3506
Translational invariance <sup>a</sup>	x	0.0000	0.0023	0.0000	-0.0017
	y	0.0001	-0.0008	0.0000	0.0005
	z	0.0000	0.0012	-0.0003	0.0021

<sup>a</sup> Taking into account nonreported coordinates.

they must be taken into account when computing the gradient of molecular energy in solution.

An important test of the reliability of calculated derivatives is their translational invariance—namely, the sum of the derivatives with respect to the same coordinate for all the atoms. This sum should be zero, as it corresponds to an overall translation of the solute. The data reported in Tables II through IV show that the invariance of the analytical derivatives is satisfactory, even better than that of numerical results. Moreover, the analytical derivatives of solvent excluding surfaces are of the same quality as the derivatives of accessible surfaces: This means that the added spheres used to define the solvent excluding surfaces do not create any problem in the calculations.

In Table V some results of the derivatives of the dispersion and repulsion energies in water are listed. Only the coordinates with the largest derivatives have been reported: The agreement with the numerical calculations is good. The mag-

nitude of these derivatives is small, but we expect that their contribution to the free energy gradient becomes important for nonpolar solutes in media of low dielectric constant. This provision will be checked in a further work, when the present procedure will be applied to the other components of free energy in solution and then used in geometry optimizations of molecules in solution.

Finally, a comment about the computational times: The calculation of analytical derivatives has proved effective. In the case of  $\text{H}_2\text{O}$ , the definition of the solvent excluding surface takes 0.05 s of central processing unit (CPU) time (on an IBM Risk 6000/58H), exactly the same time needed for calculation of the derivatives with respect to all the nine nuclear coordinates. In the case of propane in water, the surface is defined in 0.29 and the 33 derivatives are calculated in 0.71 s. In any case, these times are completely negligible compared to the CPU times needed for self-consistent field (SCF) calculations on the same molecules.

TABLE V.

Analytical Derivatives of Dispersion and Repulsion Energies for  $\text{H}_2\text{O}$ ,  $\text{CH}_3\text{CH}_2\text{CH}_3$ , and  $\text{CH}_3\text{CHO} \cdots \text{H}_2\text{O}$  with Respect to Some Atomic Coordinates, Compared to Numerical Derivatives (see Fig. 11 for the Atomic Labels).

Molecule	Atom	Coord.	Derivatives of dispersion energy ( $\times 10^3$ au)		Derivatives of repulsion energy ( $\times 10^3$ au)	
			Analytical	Numerical	Analytical	Numerical
$\text{H}_2\text{O}$	O	x	0.023	0.020	0.008	0.007
		y	-0.001	0.0	0.005	0.006
		z	0.007	0.007	-0.011	-0.011
	$\text{H}_1$	x	-0.009	-0.009	0.003	0.003
		y	0.011	0.009	0.010	0.009
		z	0.002	0.002	0.001	0.001
$\text{CH}_3\text{CH}_2\text{CH}_3$	$\text{C}_1$	x	-0.003	-0.002	0.002	0.001
		y	0.001	0.001	-0.002	-0.002
		z	0.019	0.018	-0.015	-0.012
	$\text{H}_1$	x	0.001	0.0	0.003	0.003
		y	-0.020	-0.021	0.011	0.010
		z	-0.004	-0.004	-0.001	-0.001
	$\text{H}_5$	x	-0.004	-0.004	0.009	0.009
		y	-0.012	-0.010	0.008	0.006
		z	0.001	0.001	-0.002	-0.002
	$\text{C}_1$	x	-0.011	-0.010	0.005	0.005
		y	0.004	0.004	0.003	0.002
		z	0.012	0.011	-0.010	-0.009
$\text{CH}_3\text{CHO} \cdots \text{H}_2\text{O}$	$\text{O}_1$	x	0.002	0.002	0.001	0.001
		y	0.008	0.009	-0.012	-0.010
		z	-0.003	-0.003	0.005	0.005
	$\text{H}_5$	x	-0.003	-0.002	0.007	0.007
		y	-0.013	-0.013	-0.001	-0.002
		z	0.009	0.007	0.003	0.003

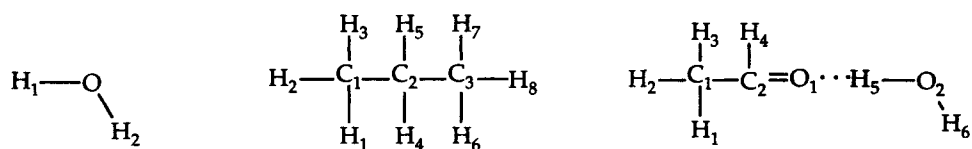


FIGURE 11. Atomic labels for the molecules used as examples.

## Conclusions

We have presented a general and reliable procedure for the analytical calculation of derivatives of the area and other geometrical quantities of the solute molecular surface, with respect to solute nuclear coordinates. The application of this algo-

rithm to the case of solute-solvent dispersion-repulsion interactions shows that it is effective in calculation of the energy gradient for molecules in solution, in the framework of the PCM model. This procedure has been applied to the other components of the solute-solvent interaction (i.e., electrostatic and cavitation energies),<sup>27</sup> thus providing a routine method to calculate free energy gradients for molecules in solution.

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## Appendix

Let us introduce a scaling parameter  $\lambda$  in eq. (11) [for  $\lambda = 1$ , one obtains eq. (11)]:

$$S_i = S_i(\lambda R_I, \lambda C_I, \{\lambda R_K\}, \{\lambda C_K\}) \quad (63)$$

An infinitesimal change  $dR_I$  of the radius  $R_I$  can be expressed in terms of  $d\lambda$ ,  $dC_I$ ,  $\{dR_K\}$ , and  $\{dC_K\}$  if

$$\begin{aligned} S_i(\lambda(R_I + dR_I), \lambda C_I, \{\lambda R_K\}, \{\lambda C_K\}) \\ = S_i((\lambda + d\lambda)R_I, (\lambda + d\lambda)(C_I + dC_I) \\ \times \{(\lambda + d\lambda)(R_K + dR_K)\}, \\ \times \{(\lambda + d\lambda)(C_K + dC_K\})) \end{aligned} \quad (64)$$

The latter condition is fulfilled if

$$\begin{cases} (\lambda + d\lambda)R_I = \lambda(R_I + dR_I) \\ (\lambda + d\lambda)(C_I + dC_I) = \lambda C_I \\ (\lambda + d\lambda)(R_K + dR_K) = \lambda R_K \quad \forall K \\ (\lambda + d\lambda)(C_K + dC_K) = \lambda C_K \quad \forall K \end{cases} \quad (65)$$

Neglecting the products of infinitesimal quantities, eq. (65) becomes

$$\begin{cases} d\lambda = -\frac{\lambda}{R_I} dR_I \\ dC_I = -\frac{C_I}{R_I} dR_I \\ dR_K = -\frac{R_K}{R_I} dR_I \quad \forall K \\ dC_K = -\frac{C_K}{R_I} dR_I \quad \forall K \end{cases} \quad (66)$$

Then we can write

$$\begin{aligned} \frac{\partial S_i}{\partial R_I} = \frac{\partial \lambda}{\partial R_I} \frac{\partial S_i}{\partial \lambda} + \frac{\partial C_I}{\partial R_I} \cdot \vec{\nabla}_I S_i \\ + \sum_K \left[ \frac{\partial R_K}{\partial R_I} \frac{\partial S_i}{\partial R_K} + \frac{\partial C_K}{\partial R_I} \cdot \vec{\nabla}_K S_i \right] \end{aligned}$$

$$\begin{aligned} = \frac{\lambda}{R_I} \frac{\partial S_i}{\partial \lambda} - \frac{C_I}{R_I} \cdot \vec{\nabla}_I S_i \\ - \sum_K \left[ \frac{R_K}{R_I} \frac{\partial S_i}{\partial R_K} + \frac{C_K}{R_I} \cdot \vec{\nabla}_K S_i \right] \end{aligned} \quad (67)$$

where  $\vec{\nabla}_I$ ,  $\vec{\nabla}_K$  indicate the gradients with respect to the coordinates of the centers of  $I$  and  $K$ , respectively.

Because tesserae are parts of spherical surfaces, it is easy to see that

$$\frac{\partial S_i}{\partial \lambda} = \frac{2S_i}{\lambda} \quad (68)$$

Moreover, eq. (13) shows that

$$\vec{\nabla}_I S_i = - \sum_K \vec{\nabla}_K S_i \quad (69)$$

Substituting eqs. (68) and (69) in eq. (67), we can write

$$\frac{\partial S_i}{\partial R_I} = \frac{2S_i}{R_I} - \sum_K \left[ \frac{R_K}{R_I} \frac{\partial S_i}{\partial R_K} + \frac{C_K - C_I}{R_I} \cdot \vec{\nabla}_K S_i \right] \quad (70)$$

corresponding to eq. (14) in the text.

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